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PATENT SPECIFICATION

689,835

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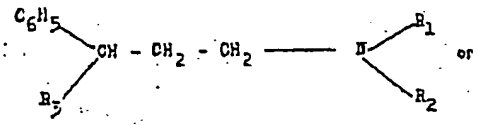
COMPLETE SPECIFICATION

Manufacture of Para-Aminosalicylates

We, MICHAEL ERLENBACH and ADOLF SIEGLITZ, both German citizens, of Georg Voigtsstrasse 12, Frankfurt, Main, Germany, and Oriensstrasse, Bad Soden, Taunus, Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The usual anti-histaminic substances are generally applied for therapeutic purposes in the form of salts of the corresponding bases with inorganic acids, the potency of the salt corresponding to that of the base diminished in proportion to the weight of the acid combined with the base. (Compare "Die Pharmazie," 1947, page 495; "Chemisches Zentralblatt," Verlag Chemie, 1947, Vol. I, pages 446 *et seq.*).

The present invention is based on the observation that the salts of anti-histaminic bases of the general formula



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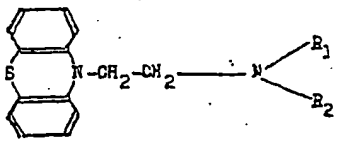

in which R_1 and R_2 each represents a methyl group or the grouping

represents a pyrrolidino group, and R_3 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid are distinguished by a surprisingly high anti-histaminic action. This action considerably exceeds that of the anti-histaminic base and the known salts thereof.

Although para-aminosalicylic acid itself exhibits a certain anti-histaminic effect, this does not suffice to explain the enhanced action of the salts, which is due to a synergistic action.

The salts of anti-histaminic bases with para-aminosalicylic acid are made in accordance with this invention by reacting equimolecular proportions of para- aminosalicylic acid with an anti-histaminic base, or by the double decomposition of an alkali salt or alkaline earth metal salt of para-aminosalicylic acid with a salt of an anti-histaminic base with an inorganic acid.

As examples of salts of anti-histaminic bases in accordance with the invention there may be mentioned especially 1-phenyl-1-pyridyl - (2^1) - 3-dimethylaminopropane para-aminosalicylate, 1-phenyl-1-pyridyl-(2^1)-3-N-pyrrolidinopropane para - aminosalicylate, 1-phenyl - 1 - thiazolyl - (2^1) - 3-N-pyrrolidino-propane para-aminosalicylate and 10-dimethyl-aminoethyl-phenthiazine para-aminosalicylate.

The following examples illustrate the invention, the parts being by weight unless otherwise stated, and the relationship of parts by weight to parts by volume being the same as that of the kilogram to the litre:

EXAMPLE 1.

1-PHENYL-1-PYRIDYL-(2^1)-3-DIMETHYLAMINO-PROPANE PARA-AMINOSALICYLATE.

Equivalent quantities of 1-phenyl-1-pyridyl-(2^1) - 3 - dimethyl - aminopropane and para-aminosalicylic acid are separately dissolved in ethyl acetate, and the two solutions are mixed together. The salt named above very soon separates in a practically quantitative yield. It melts at temperatures of 144—145° C. with decomposition, and is twice as potent as the corresponding phosphate.

EXAMPLE 2.

1-PHENYL-1-PYRIDYL-(2^1)-3-N-PYRROLIDINO-PROPANE PARA-AMINOSALICYLATE.

5.32 parts of 1-phenyl-1-pyridyl-(2^1)-3-N-

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pyrrolidino-propane are dissolved in 40 parts by volume of acetone, and 6.12 parts of para-aminosalicylic acid are dissolved in 30 parts by volume of acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates which melt at 171—172° C. with decomposition. The yield is nearly quantitative. The para-amino-salicylate is soluble in water and about twice as potent as the corresponding phosphate.

EXAMPLE 3.

1 - PHENYL - 1 - THIAZOLYL - (2') - 3 - N-PYRROLIDINOPROPANE PARA-AMINOSALICYLATE.

Equivalent quantities of para-aminosalicylic acid and 1-phenyl - 1 - thiazolyl - (2') - 3 - N-pyrrolidinopropane are separately dissolved in acetone, and the two solutions are mixed together. After standing for some time, the para-aminosalicylate crystallises in the form of plates melting at 161—162° C. with decomposition. The yield is practically quantitative. The product is soluble in water and twice as potent as the corresponding phosphate.

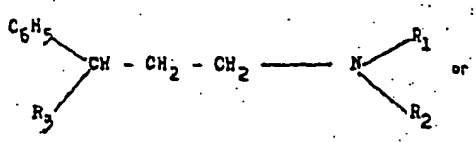
EXAMPLE 4.

10-DIMETHYLAMINOETHYL-PHENTHIAZINE PARA-AMINOSALICYLATE.

10 parts of 10-dimethylaminoethyl-phenthiazine hydrochloride are dissolved, while gently heating, in 120 parts of water, and the solution so obtained is mixed with a solution of 7 parts of sodium para-amino-salicylate in 50 parts by volume of water. The oily solution, which separates, rapidly becomes solid on rubbing. 13.3 parts of the para-aminosalicylate are obtained as a colourless salt which is sparingly soluble in water and readily soluble in hot acetone, in hot methyl alcohol and in ethyl acetate. It decomposes at 159—160° C. and is twice as potent as the hydrochloride of 10 - dimethyl - aminoethyl-phenthiazine.

What we claim is:—

1. A salt of an anti-histaminic base of the general formula



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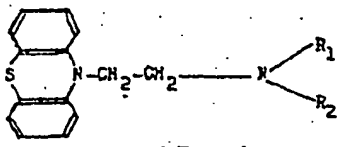
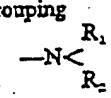


in which R_1 and R_2 each represent a methyl group or the grouping



represents a pyrrolidino group, and R_3 represents a pyridyl or thiazolyl group, with para-aminosalicylic acid.

2. 1-Phenyl - 1 - pyridyl-(2')-3-dimethyl-amino-propane para-aminosalicylate.

3. 1-Phenyl-1-pyridyl-(2')-3-N-pyrrolidino-propane para-aminosalicylate.

4. 1-Phenyl - 1 - thiazolyl-(2')-3-N-pyrrolidinopropane para-aminosalicylate.

5. 10 - Dimethylaminoethyl - phenthiazine para-aminosalicylate.

6. A process for the manufacture of a salt of an anti-histaminic base claimed in any one of claims 1—5, wherein para-aminosalicylic acid and the anti-histaminic base are reacted together in equimolecular proportions or an alkali salt or an alkaline earth metal salt of para-aminosalicylic acid is reacted with a salt of the anti-histaminic base with an inorganic acid.

7. A process for the manufacture of a salt of an anti-histaminic base conducted substantially as described in any one of Examples 1—4 herein.

ABEL & IMRAY,
Agents for the Applicants,
Quality House, Quality Court, Chancery Lane, W.C.2.

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